doi 10.18699/bgrs2024-2.1-14

Analysis of the evolution of the human genes encoding cell surface receptors involved in the regulation of appetite using phylostratigraphic age and divergence indexes

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Key words: regulation of appetite; cell surface receptors; hunger; evolution; phylostratigraphic analysis; gene age; gene variability

Motivation and Aim: Appetite is a drive to consume food. It is one of the most primitive instincts promoting survival and it exists in all higher life-forms. Appetite serves to regulate adequate energy intake to maintain metabolic needs, although it may be stimulated by appealing foods even when hunger is absent. Dysregulation of appetite can lead to human diseases (bulimia nervosa and overeating (both leading to obesity), anorexia nervosa, cachexia, etc.) [1]. Understanding the evolutionary mechanisms of human diseases, especially those related to lifestyle changes that have occurred over the past 100–200 years, is of fundamental and applied importance. It is also very important to identify relationships between the evolutionary characteristics of genes in gene networks and the resistance of these networks to changes caused by mutations. We have previously analyzed the evolutionary characteristics of genes involved in networks from the KEGG Pathway, Human Diseases database describing various human diseases [2]. The features of these networks have been identified both in the context of the phylostratigraphic age (time of gene origin) of their constituent genes and the nature of the selection to which they are subjected (stabilizing or driving) [2]. On the other hand, we have previously performed a functional analysis of genes involved in the regulation of appetite and body weight [3, 4]. When analyzing a set of 105 genes involved in appetite regulation, a statistically significant over-enrichment of genes specifically expressed in the brain was found. It was also revealed that a substantial proportion of genes (~45 %) in this set were genes encoding cell surface receptors. Many of these receptors belonged to the superfamily of G-protein-coupled receptors (GPCRs). Thus, the aim of the current study is to identify the distinctive features of human genes encoding cell surface receptors involved in appetite regulation using the phylostratigraphic age index (PAI) and divergence index (DI).
Methods and Algorithms: A set of human receptor genes whose orthologues were involved in appetite regulation in model organisms was formed based on the analysis of scientific publications. Evolutionary characteristics of genes (phylostratigraphic age index (PAI) and divergence index (DI)) have been calculated as it was described in [2] taking into account sequences of orthologous genes that are 50 % or more identical to one under consideration. To identify genes involved in the control of biological processes related to development we used annotation of genes by GO terms obtained from DAVID tool [5].

Results: We found 80 human genes orthologous to genes identified in model organisms and encoding cell surface receptors. It turned out that the set of genes under consideration contains an increased number of genes (37) with the same phylostratigraphic age (PAI=6, the stage of vertebrate divergence), and almost all of these genes (35 out of 37) belong to the superfamily of G-protein coupled receptors. Apparently, the synchronized evolution of such a large group of genes (37 genes out of 80) is associated with the development of the brain as a separate organ in the first vertebrates.
When studying the distribution of genes from the same set by DI values, a significant enrichment with genes that had low DIs was revealed. Eleven genes (*GPR26*, *NPY1R*, *GHSR*, *CNR1*, *ADIPOR1*, *DRD1*, *MCHR1*, *ADCYAP1R1*, *NPY2R*, *GPR171*, and *NPBWR1*) had an extremely low DIs (less than 0.05). Such low values of DI indicate that these genes are very likely exposed to stabilizing selection. The lowest DI was found for *GPR26*. Due to the fact that the endogenous ligands for the GPR26 receptor had not yet been identified yet, this gene seems to be an extremely interesting object for further theoretical and experimental research. It was also found that the group of genes with low DIs was enriched with genes that were related to development.
Conclusion: We believe that the features of genes encoding cell surface receptors we have identified using PAI and DI evolutionary metrics can be a the starting point for further evolutionary analysis of the gene network regulating appetite.
Funding: The study is supported by publicly funded project No. FWNR-2022-0020 of the Federal Research Center ICG SB RAS.

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